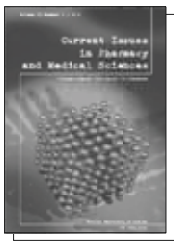

2012 Curr. Issues Pharm. Med. Sci. Vol. 25, No. 1

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy

Influence of sterilization on the rheological properties of different types polyacrylic acid gels

ANNA KODYM, BARTŁOMIEJ KUBIAK*, KAROLINA MISZK, JOANNA RONOWICZ, ŁUKASZ PAŁKOWSKI

Department of Pharmaceutical Technology, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Poland

ABSTRACT

The aim of the study was to analyze the influence of sterilization conditions on the rheological properties of gels containing polyacrylic acid derivatives (Carbopols: 974P, Ultrez 10 and Ultrez 20). The gels utilized in this study contained 0.5% (w/w) metronidazole, antiprotozoal drug (model drug substance). Their rheological properties were determined: flow curve, yield point, apparent viscosity. Moreover, a statistical analysis of factors (polymer type, polymer concentration, sterilization by autoclaving) was undertaken, and their impact on viscosity, yield point and area under flow curve was ascertained. Among this polymers, gels comprising Carbopol 974P were the most stable to sterilization conditions.

Keywords: rheology, ophthalmic gel, Carbopol

INTRODUCTION

Carbomers are a group of polymers (consisting of acrylic acid) widely used in pharmaceutical technology, where they are employed as: emulsifying agents, dispersion stabilizing agents, modified-release agents, suspending agents and viscosity-increasing agents [6]. These polymers are very popular in semisolid formulations due to their low toxicity and the relatively low concentrations in which they are used. Among these Carbomer formulations are the many commercial ophthalmic products available today (eye drops and gels). Such viscous eye drops and eye gels are used to obtain prolonged contact time to the cornea and to sustain the release of API. In this employment, the residence time of the gel in the conjunctival sack, is not only result of increased viscosity (high viscosity induces irritation), but is also due to the effect of adhesion to the mucin layer of the tear film (muocadhesion). Bioadhesive polymers (including Carbomers) are, therefore, preferred in ophthalmic formulations and in drugs for any other mucosa [5].

One of the fundamental pharmacopoeial requirements for any ophthalmic preparation is sterility. The most effective method of sterilization of water solutions is by way of steam sterilization in an autoclave. However, not all polymers solutions may be treated with this method of sterilization e.g. hydroxypropyl cellulose, carboxymethyl cellulose sodium, cannot be sterilized by moist heat. In previous research, it has been noted that Carbopol-based gels have demonstrated minimal viscosity changes during sterilization. However, the literature data is based on studies using Carbopol 940, 934 or 974 [6, 7], and these come from the 70's-80's of the past century [1, 4]. Therefore, we have investigated the effect of sterilization on newer polymer varieties, namely Carbopol Ultrez 10 and 20.

Corresponding author
* Department of Pharmaceutical Technology, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, 2 Jurasza Str., 85-089 Bydgoszcz, Poland
e-mail address: bartlomiej.kubiak@cm.umk.pl

MATERIALS AND METHODS

Polymers Carbopol: 974P (C974), Ultrez 10 (CU10), Ultrez 20 (CU20) Lubrizol Corp. (Cleveland, USA) were obtained from S&D Poland, Mannitol, NaOH were purchased from POCH (Gliwice, Poland), benzalkonium chloride was purchased from Pharma-Cosmetic (Kraków, Poland), metronidazole was obtained from ZF Polpharma (Starogard Gdański, Poland).

To prepare a Carbopol gel, the required amount of the polymer was dispersed in an isoosmotic metronidazole 0.5% (w/w) and mannitol 5.0% (w/w) solution. Dispersion was neutralized to pH below 7.0 by adding a NaOH solution 10% (w/w). Benzalkonium chloride was then used as a preservative with final concentration 0.006 % (w/w). After 24h, the pH was adjusted to 7.0. After this, the gels were autoclaved (121°C, 20 min., 101.4 kPa). Data was collected before and after sterilization.

The rheological properties were measured by using a cone and plate rotational rheometer Rheotest RN4 CS CR (Rheotest Messgeräte, Medingen, Germany). A cone K3 with a diameter of 36 mm and an aperture angle between cone and plate of 1°, was used. The measuring system was thermostatic, the temperature of the sample was 20°C.

The CR mode was used to obtain flow curves (0 to 100 1/s), while apparent viscosities (η_{100}) were read from flow curves. The area under the flow curve (AUR) was calculated with Kinetica 4.2 software (Thermo LabSystems) (some authors, however, opine that this factor can be more sensitive than the viscosity value [8]). Moreover, the yield point was measured by way of the CS mode. Data was collected before and after sterilization. The obtained results were statistically analyzed with Statistica software (StatSoft).

RESULTS AND DISCUSSION

CU10 and CU20 belong to the new self-wetting polymers group. Because of the attributes exhibited by this group, they shorten the time of preparation of the dispersion, and consequently, the time of preparation of the gel. The specific properties of the Carbopols result from their cross-linking effects (the type of cross-linking substance, the density of the bonds), the solvent used during synthesis and the modification of the molecule (homopolymer, copolymer). C974P is a homopolymer cross-linked with glucose and allyl ethers of pentaerytritol, the density of these bonds is defined as medium. CU10 is defined as a carbomer homopolymer or copolymer that contains a block copolymer of polyethylene glycol and long-chain alkyl esters. The density of bonds is defined as high, whereby prepared gels are characterized by high viscosity. CU20 is a long chain alkyl acrylate copolymer with a modified molecular structure that gives it an amphiphilic character and increases its resistance to ions [3, 7].

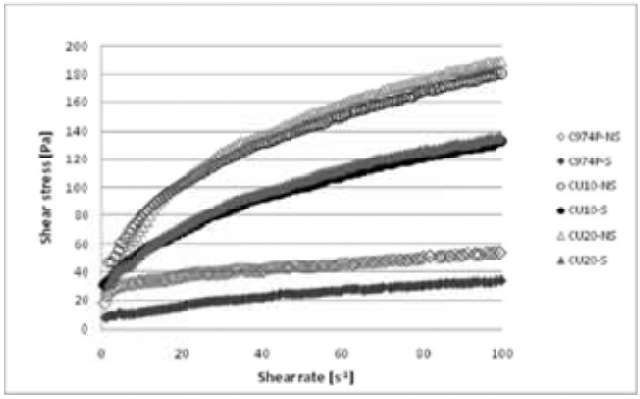

Fig. 1. Flow curves of 0.25% Carbopol gels

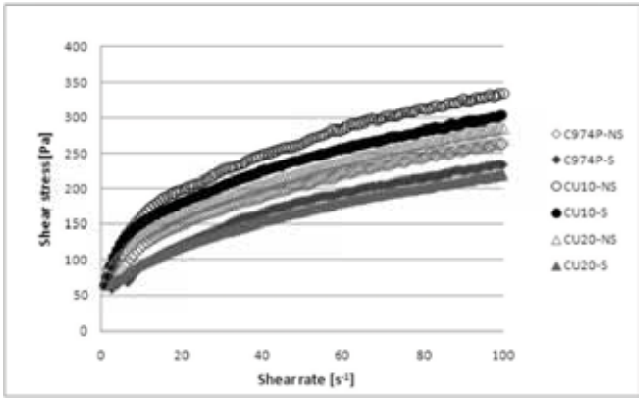

Fig. 2. Flow curves of 0.5% Carbopol gels

These gels exhibit non-Newtonian, plastic flow properties (Fig. 1 and 2), with yield point below 70 and 30 Pa for gels with polymer concentrations of 0.5% and 0.25% respectively. To study the statistical significance of differences between mean values of the various rheological parameters (yield point, viscosity, AUR), multifactorial analysis of variance was performed. In doing this, the simultaneous influence of 3 factors on rheological properties were examined:

- type of gelling agent (C974P, CU10, CU20),
- concentration of gelling polymer (0.25% and 0.5%),
- sterilization step (non-sterile NS, sterile S).

The advantage of multifactorial analysis of variance is that it provides the ability to detect the possible effect of interaction: that is, the cooperation of the analyzed factors on the results of the experiment. In this regard, normal probability plots and the normality test of Shapiro-Wilk ($p > 0.05$)

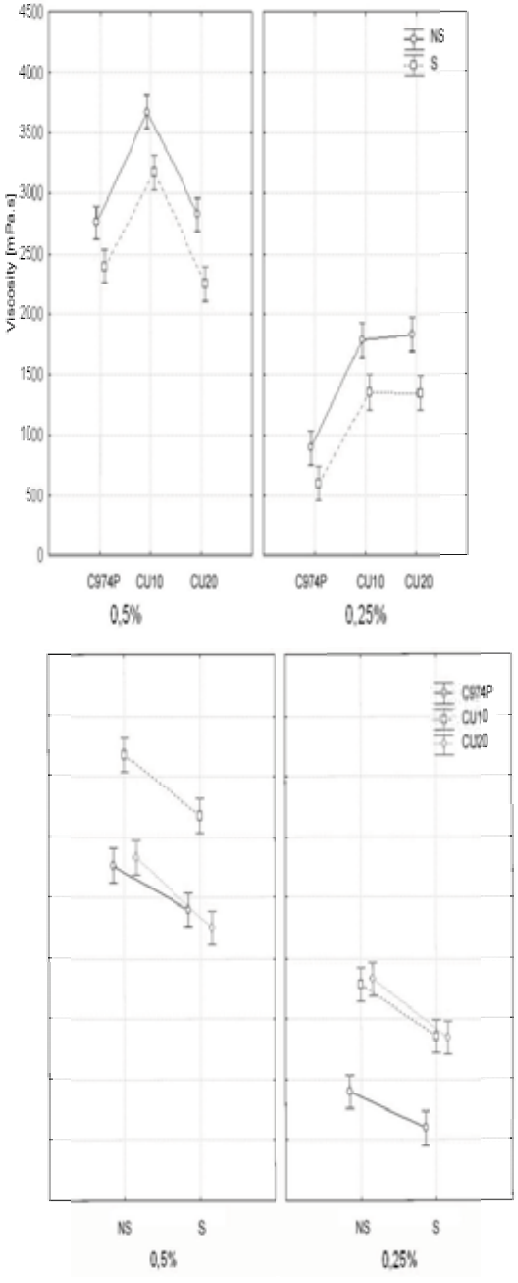

Fig. 3. Mean viscosity value of prepared gels

confirmed the absence of statistically significant deviations from the empirical distribution of the theoretical distribution function of the Gaussian as described. Furthermore, the ANOVA analysis of variance was employed to test average viscosity gels (D = 100 s^{-1}) according to the mentioned earlier three factors. This showed that there are significant differences in the mean values of viscosity of the formulations tested, due to their sterilization in an autoclave. These differences are also a result of using different types of Carbopol and their various concentrations in the formulations. Thus, all three factors affect the average values of the analyzed dependent variable ($p < 0.05$).

The interaction between the three factors analyzed did not occur. This is evident in the this value of the relevance coefficient ($p > 0.05$) and in the parallel lines on the graph as shown. Thus, these factors are additive. To examine which of the considered averages are different (analysis of the differences between the averages of each group) multiple comparison tests were used, the so-called 'post-hoc test'. These methods are useful in clarifying the nature of the differences detected earlier by analysis of variance.

Post-hoc test results revealed the presence of homogeneous groups within the data. Each homogeneous group is comprised of the formulations for which the average viscosity values are not significantly different from each other. A Tukey test showed that for formulations made on the basis of C974P at a concentration of 0.25%, there are no statistically significant differences in the mean viscosity of the gels (NS and S). Moreover, the application to the calculations of the more conservative Scheffé test, indicates that sterilization does not cause significant changes in the mean viscosity values for formulations made on the basis of C974P concentrations of both 0.25% and 0.5%, and in the case of formulations based on CU10 polymer concentration of 0.25%. The

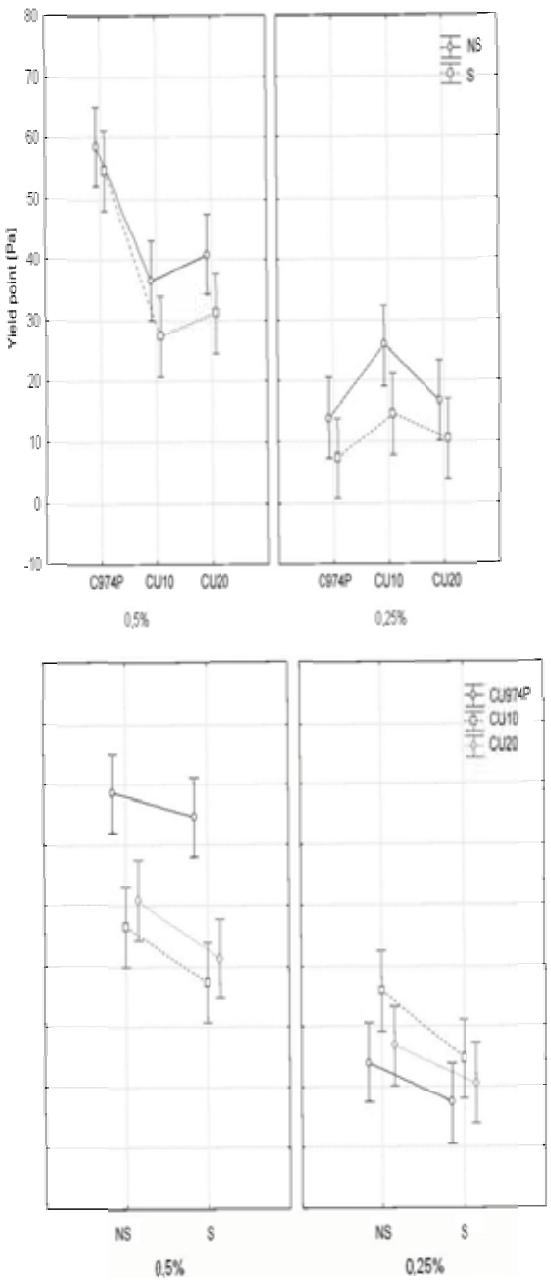

Fig. 4. Mean value of yield points

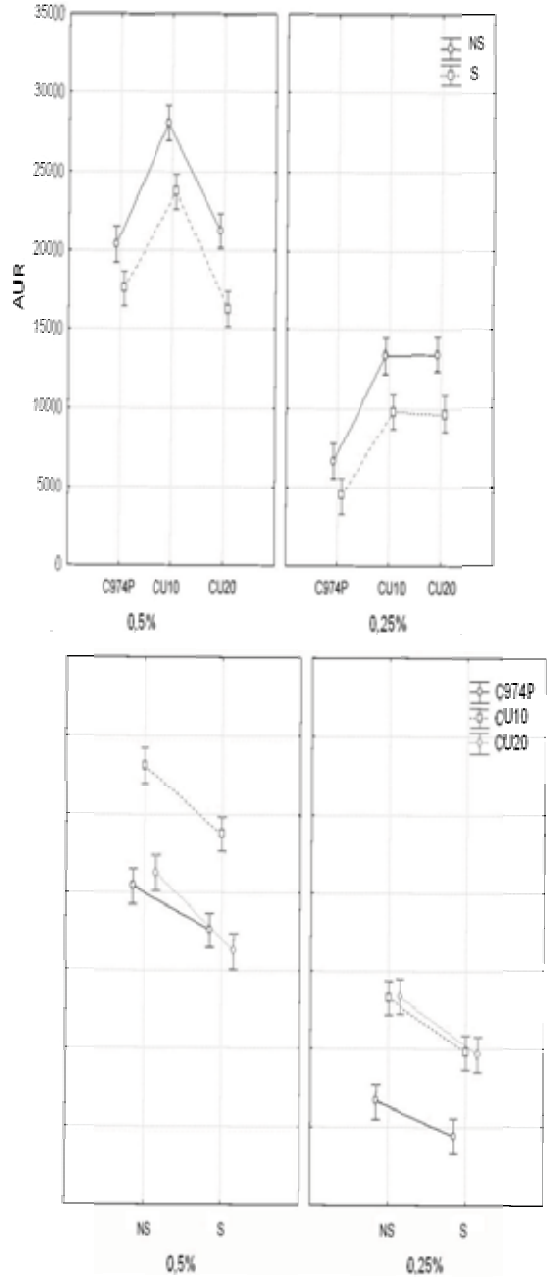

Fig. 5. Mean value of AUR

Scheffé test, being more conservative, maintains the null hypothesis, which shows no significant difference between the averages. Bindal and al. (2003) have however, observed a small increase of apparent viscosity in Carbopol 940 gels after sterilization, but their experiment was performed on small polymer concentrations (0.05%, 0.075%, 0.1%) [2]. Higher polymer concentrations in this regard, provide different results, because their polymer chains cannot freely convert to uncoil forms [3].

In regard to an analysis of the yield point, both the Tukey test and the Scheffé test showed no significant differences (for formulations made with the same concentration and type of Carbopol), before and after sterilization. The differences, which were revealed previously in the conducted analysis of variance ANOVA, therefore, result from the different grades of Carbopol and theirs various concentrations in the formulations.

The analysis of the AUR Tukey test showed that for formulations with 0.25% C974P, there are no statistically significant differences in mean values of AUR (NS and S). On the other hand, the Scheffé test indicates that sterilization does not cause a significant change in the average value of AUR of formulations of both 0.25% and 0.5% C974P, and in the case of formulations based on the CU10 polymer, at a concentration of 0.25%.

Furthermore, gels containing C974P were the least sensitive to sterilization among all the tested formulations. C974P gels containing 0.5% polymer are also characterized by having the highest yield point, whereas, CU10 and CU20 gels with 0.25% polymer content do not differ in properties. Analysis of the AUR gave similar results as the analysis of viscosity value.

Acknowledgement

This study was supported by the research grant no. 03/2008 from the Nicolaus Copernicus University, Toruń, Poland.

REFERENCES

1 Adams I. and Davis S.S.: Formulation and sterilization of an original lubricant gel base in carboxypolymethylene. *J. Pharm. Pharmacol., 25*, 640, 1973.

2 Bindal A. et al.: Effect of steam sterilization on the rheology of polymer solutions. *Pharm. Dev. Technol., 8*, 219, 2003.

3 Desai D. D., Hasman D.F. and Schmucker-Castner J.F.: Advance in Carbomer Polymer Technology. *BF Goodrich documentation*, 1996.

4 Deshpande S. G. and Shirolkar S.: Sustained release ophthalmic formulations of pilocarpine. *J. Pharm. Pharmacol.,* 41, 197, 1989.

5 Ludwig A.: The use of muco-adhesive polymers in ocular drug delivery. *Adv. Drug Deliv. Rev.,* 57, 1595, 2005.

6 Rowe R.C., Sheskey P.J. and. Owen S.C. (eds.): Handbook of Pharmaceutical Excipients 5th Ed., APhA, London and Chicago 2005.

7 Schaub A.F.: Novel Composition For Easing Human Childbirth. *Patent US2008103214*, 2008.

8. Zatloukal Z. and Šklubalová Z.: Sterilized Ophthalmic Hydrogels with Hydroxypropyl Methylocellulose: Determination and Mathematical Treatment of Flow Properties. *Pharm. Dev. Technol.,* 12, 55, 2007.